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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/831,108	01/15/2002	Stein Ove Doskeland	Q-64374	8288

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EXAMINER	
YANG, NELSON C	
ART UNIT	PAPER NUMBER
1641	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/831,108	DOSKELAND ET AL.	
	Examiner	Art Unit	
	Nelson Yang	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 April 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-8,10-14,21 and 23-27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-8, 10-14, 21, 23-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *15 January 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on April 11, 2007 has been entered.

Response to Amendment

2. Applicant's amendment of claims 4, 21, and 25 is acknowledged and has been entered.

3. Claims 2-8, 10-14, 21, 23-27 are currently pending.

Priority

4. Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Specification

5. Applicant is reminded of the proper language and format for an abstract of the disclosure.

The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 150 words. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

The language should be clear and concise and should not repeat information given in the title. It should avoid using phrases which can be implied, such as, "The disclosure concerns," "The disclosure defined by this invention," "The disclosure describes," etc.

The abstract of the disclosure is objected to because the abstract utilizes legal phraseology such as "said". Correction is required. See MPEP § 608.01(b).

6. The following guidelines illustrate the preferred layout for the specification of a utility application. These guidelines are suggested for the applicant's use.

Arrangement of the Specification

As provided in 37 CFR 1.77(b), the specification of a utility application should include the following sections in order. Each of the lettered items should appear in upper case, without underlining or bold type, as a section heading. If no text follows the section heading, the phrase "Not Applicable" should follow the section heading:

(a) TITLE OF THE INVENTION.
(b) CROSS-REFERENCE TO RELATED APPLICATIONS.
(c) STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT.
(d) THE NAMES OF THE PARTIES TO A JOINT RESEARCH AGREEMENT.
(e) INCORPORATION-BY-REFERENCE OF MATERIAL SUBMITTED ON A COMPACT DISC.
(f) BACKGROUND OF THE INVENTION.
    (1) Field of the Invention.
    (2) Description of Related Art including information disclosed under 37 CFR 1.97 and 1.98.
(g) BRIEF SUMMARY OF THE INVENTION.
(h) BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWING(S).
(i) DETAILED DESCRIPTION OF THE INVENTION.
(j) CLAIM OR CLAIMS (commencing on a separate sheet).
(k) ABSTRACT OF THE DISCLOSURE (commencing on a separate sheet).
(l) SEQUENCE LISTING (See MPEP § 2424 and 37 CFR 1.821-1.825. A "Sequence Listing" is required on paper if the application discloses a nucleotide or amino acid sequence as defined in 37 CFR 1.821(a) and if the required "Sequence Listing" is not submitted as an electronic document on compact disc).

While the specification appears to include all the above required sections, the sections are not labeled, and are not in order.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 2-8, 10-14, 21, 23-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Whitehead et al. [US 4,554,088] in view of Ward et al. [Ward et al., Colorimetric protein phosphatase inhibition assay of laboratory strains and natural blooms of cyanobacteria: comparisons with high performance liquid chromatographic analysis for microcystins, 1997, FEMS Microbiology Letters, 153, pp. 465-473] and Zhao et al. [Zhao et al., A protein phosphatase-1-binding motif identified by the panning of a random peptide display library, 1997, J Biol Chem, 272(45), pp. 28368-28372].

9. With respect to claim 21, Whitehead et al. teach a method for isolation of molecules by placing selective bioaffinity adsorbents (first ligand) on magnetic particles to which labeled ligates (second ligand) and nonlabeled ligates will bind, separating the bound ligates from free ligates, and the label measured (column 15, lines 1-45). Whitehead et al. further teach that the ligand /ligates may include enzyme/inhibitors (column 7, lines 25-35, column 17, Table III). Whitehead et al. also teach that this enables the efficient isolation of molecules (column 17, lines 16-25). Whitehead et al. further teach that the amount of unlabeled ligand can be determined by collecting the ligand-labeled ligand complex and measuring the label, and using a standard curve to determine the amount of unlabeled ligate (column 15, lines 35-40). While Whitehead et al. teaches a generic assay for the detection of inhibitors of enzymes, Whitehead et al. fail to

specifically teach an assay for a phosphatase-targeting toxin involving immobilized protein phosphatase.

Ward et al., however, teach a colorimetric protein phosphatase inhibition assay for microcystins using protein phosphatases (p.467, col. 1). Ward et al. further teach that microcystins are a group of cyclic heptapeptide hepatotxins capable of being produced by common bloom-forming genera of cyanobacteria (p.465, col.1), and which bind irreversibly to and inhibit protein phosphatases 1 and 2A (p.465, col.2). Ward et al. further teach that due to the increased awareness of the hazards presented by these toxins, increasingly sensitive detection methods are required to provide information for the effective management of waters supporting cyanobacterial blooms (p.466, col.1, pg.2).

Furthermore, one of ordinary skill in the art at the time of the invention would have had a reasonable expectation of success in adapting the method of Whitehead et al. to protein phosphatases such as protein phosphatase 1 for detection of toxins. In particular, Zhao et al. disclose a means for immobilizing protein phosphatase 1 wherein adsorption is confirmed by testing for activity of the bound enzyme toward phosphorylase a (p. 28368, col.2, para. 5). Zhao et al. further tested several synthetic peptides for their ability to inhibit the activity of the immobilized PP1 (p.28370, col.1, para. 2).

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to have utilized the method of Whitehead et al. to detect specific inhibitors such as microcystins, as suggested by Ward et al., by using an enzyme such as a protein phosphatase as the bioaffinity adsorbent, because the method of Whitehead et al. is generic with respect to the analytes that can be detected and the specific binding reagents that can be used and would be

motivated to use the appropriate reagents (protein phosphatases) to detect the desired analyte (microcystins), in the method of Whitehead et al.

10. With respect to claims 2-3, Ward et al. teach that microcystins are a group of cyclic heptapeptide hepatotxins capable of being produced by common bloom-forming genera of cyanobacteria (p.465, col.1),

11. With respect to claims 4, 11, Whitehead et al. teach that the labeled ligate and nonlabeled ligates compete for binding to the ligand (column 15, lines 28-45). Since Ward et al. teach the use of protein phosphatases as the enzymes to detect toxins such as microcystins (p.466, col.1, pgs.2-3), the labeled ligate and nonlabeled ligates would be labeled and nonlabeled microcystins, which are heptapeptide hepatotoxins.

12. With respect to claim 5, Whitehead et al. teach that the amount of unlabeled ligate can be determined by collecting the ligand-labeled ligand complex and measuring the label, and using a standard curve to determine the amount of unlabeled ligate (toxin) (column 15, lines 35-40). The proportion of the labeled ligand detected would be indicative of the unlabeled ligate, as it would be proportionate.

13. With respect to claim 6, Ward et al. suggests that the detection methods are used for potable waters (p. 466, col.1, pg. 2).

14. With respect to claim 7, Whitehead et al. teach that the label may comprise an antibody wherein the amount of label is generally inversely proportional to the amount of analyte originally in the solution (column 8, lines 19-20), which in this case would be the toxins.

15. With respect to claim 8, Ward et al. teach that microcystins bind irreversibly to and inhibit protein phosphatases 1 and 2A (p. 465, col.2), demonstrating that PP1 and PP2A are

equivalent structures known in the art. Therefore, because these two were art-recognized equivalents at the time the invention was made, one of ordinary skill in the art would have found it obvious to substitute protein phosphatase 2A for protein phosphatase 1. Since the proteins belong to the same family of proteins, and have similar functions, one of ordinary skill in the art would also have had a reasonable expectation of success in substituting protein phosphatase 2A for protein phosphatase 1, since Zhao et al. disclose that immobilize protein phosphatase have activity toward phosphorylase a (p. 28368, col.2, para. 5) and further tested several synthetic peptides for their ability to inhibit the activity of the immobilized PP1 (p.28370, col.1, para. 2).

16. With respect to claim 10, Whitehead et al. teach labeled ligate (second ligand) (column 15, lines 10-15) which would contain a label (reporter moiety).

17. With respect to claim 12, Ward disclose that the microcystins to be detected include microcystin-LR (p.465, col.2).

18. With respect to claim 13, Whitehead et al. teach ligands coupled to an insoluble support or matrix (column 17, lines 20-30).

19. With respect to claim 14, Whitehead et al. teach magnetic particles (column 7, lines 5-15).

20. With respect to claims 23-24, Whitehead et al. teach that the bioaffinity adsorbents are bound to the particles covalently (direct immobilization) (column 7, lines 36-45) or through silane linkages (indirect immobilization) (column 7, lines 45-55).

21. With respect to claim 25, Whitehead et al. teach that the labeled ligate-ligand is measured (column 15, lines 38-40), which is a direct measurement of the labeled ligate (which corresponds to the second ligand) in the bound fraction.

22. With respect to claim 26, while Whitehead et al. teach that the labeled ligate-ligand complex is measured (column 15, lines 38-40), one of ordinary skill in the art could also measure the amount of unbound labeled ligate, which would allow for an indirect determination of the labeled ligate-ligand complex.

23. With respect to claim 27, Whitehead et al. teach competitive assays in which the amount of bound measaurable label is inversely proportional to the amount of analyte in solution (column 8, lines 25-40).

Response to Arguments

24. Applicant's arguments filed July 13, 2006 have been fully considered but they are not persuasive.

25. Applicant specifically argues that the techniques taught by Whitehead et al., while suitable for antibodies in a binding assay, are not generally suitable for enzymes (p.5), and that the discussion by Whitehead et al. is merely a general "prophetic" discussion, and would not render one skill in the art to have an expectation of success in immobilizing protein phosphatase on a solid support (p. 6). The Office, however, notes that Whitehead et al. cites several examples where immobilized enzyme systems are used (column 16, lines 59-65) and is merely adapting the systems from non-magnetic supports to magnetic supports. Furthermore, regardless of whether the discussion by Whitehead et al. is "prophetic" or not, all embodiments must be considered, and since Whitehead et al. disclose an embodiment involving immobilized enzymes, that embodiment must be considered Furthermore, one of ordinary skill in the art at the time of the invention would have had a reasonable expectation of success in adapting the method of Whitehead et al. to protein phosphatases such as protein phosphatase 1 for detection of toxins. In

particular, Zhao et al. disclose a means for immobilizing protein phosphatase 1 wherein adsorption is confirmed by testing for activity of the bound enzyme toward phosphorylase a (p. 28368, col.2, para. 5). Therefore, one of ordinary skill in the art at the time of the invention would have had a reasonable expectation of success in adapting the method of Whitehead et al. to protein phosphatases such as protein phosphatase 1 for detection of toxins. Since applicant has not provided any evidence that immobilized protein phosphatases would not be capable of detecting toxins in a sample, applicant's arguments are not found persuasive.

26. With respect to applicant's arguments on p. 7 that the protein phosphatase 2A structure has only been recently been determined, the Office is unclear as to where in the reference provided by applicant (Xing et al.) it is disclosed. Furthermore, while the article focuses on the specific flexibility requirements of the PP2A conformation for its function, there is no evidence that one of ordinary skill in the art would not have been able to utilize PP2A in immobilized enzyme assays such as those disclosed by Whitehead et al prior to the reference.

27. With respect to applicant's argument on p. 7 that Carmichael et al. discuss the disadvantages of the enzymatic assay, and suggest that a combination of ELISA and the enzymatic assay would prove very useful in detecting many of the toxins in an environmental sample, the Office notes that this argument merely establishes the need for multiple assays in order to verify and detect the toxins present in a sample, and provides no evidence why the combination of Whitehead et al. and Ward et al. would not work in detecting the presence of protein phosphatase targeting toxins. Furthermore, it is unclear how applicant arrived at the conclusion that Whitehead et al. and Ward results at best in a "sequential" and separate use of the two methods.

28. With respect to applicant's arguments on p. 8 that Sikorska will not directly detect toxicity, the Office notes that applicant recites a method for determining the presence of a phosphatase-targeting toxin in a sample, and not toxicity of the sample. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., detecting toxicity of a sample) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

29. With respect to applicant's argument that the binding assay of the present invention provides unexpectedly superior results compared to both antibody assays and protein phosphatase inhibition assays, the Office notes that applicant would need to provide unexpected superior results compared with other immobilized enzyme assays, which are known in the art as mentioned by Whitehead et al. (column 17, table II) and Zhao et al. (abstract).

30. With respect to applicant's arguments on p. 8 that Whitehead et al. teach a simple binding assay and do not teach competition assay for the detection of a ligand, the Office notes that Whitehead et al. disclose that the term "binding assay" may be competitive or non-competitive.

31. With respect to applicant's arguments on p. 9 that the skilled reader would largely disregard the teaching of Whitehead et al. as it relates to enzymes, the Office does not find these arguments persuasive, as applicant has not provided any evidence that the enzyme based assays of Whitehead et al. would not work, and therefore, one of ordinary skill in the art would have no reason to disregard the teachings of Whitehead et al. as it relates to enzymes.

32. For these reasons, the rejections has been maintained.

Conclusion

33. No claims are allowed.

34. The following reference was cited by applicant but was not found in any of the information disclosure statements: [Xing et al, Structure of protein phosphase 2A core enzyme bound to tumor-inducing toxins, 2006 Cell 127, pp.341-353]. The reference has therefore been included in the PTO-892.

35. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nelson Yang whose telephone number is (571) 272-0826. The examiner can normally be reached on 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long V. Le can be reached on (571)272-0823. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

36. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

1/2/07

Nelson Yang
Patent Examiner
Art Unit 1641